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VIEWPOINT

The Premotor Syndrome of Cervical Dystonia: Disordered Processing of Salient Environmental Stimuli

Michael Hutchinson, FRCP [1,2*] Eavan M. McGovern, MRCPI,[1,2] Shruti Narasimham, MSc,[3] Rebecca Beck, PhD,[3] Richard B. Reilly, PhD,[3,4] Cathal D. Walsh, PhD,[5] Kevin M. Malone, FRCPsych,[2,6] Marina A.J. Tijssen, PhD, MD,[7] and Sean O'Riordan, FRCPI[1,2]

[1]*Department of Neurology, St. Vincent's University Hospital, Dublin, Ireland*
[2]*School of Medicine and Medical Sciences, University College Dublin, Dublin, Ireland*
[3]*Trinity Centre for Bioengineering, School of Engineering, Trinity College Dublin, Dublin, Ireland*
[4]*School of Medicine Trinity College Dublin, The University of Dublin, Dublin, Ireland*
[5]*Department of Mathematics and Statistics, University of Limerick, Limerick, Ireland*
[6]*Department of Psychiatry, School of Medicine and Medical Sciences, University College Dublin, Dublin, Ireland*
[7]*Department of Neurology, University Medical Center Groningen, Groningen, The Netherlands*

The Concept of the Premotor Syndrome of Cervical Dystonia

Although cervical dystonia presents clinically as a motor disorder, a nonmotor syndrome, including disordered sensory processing, neuropsychiatric, and sleep symptoms, is increasingly recognized and has been the subject of recent reviews.[1-4] The purpose of this article is to argue that: (1) This nonmotor syndrome should also be considered a "premotor syndrome," preceding the onset of the motor phenotype by many years; (2) the premotor syndrome is attributed to the same disordered processing of salient environmental stimuli which causes the motor syndrome; and (3) research into, and treatment of, this premotor/nonmotor syndrome are significant unmet needs in patients with cervical dystonia.

Our hypothesis is that the premotor and nonmotor syndromes of cervical dystonia consisting of (1) psychiatric symptoms, (2) impaired social cognition, and (3) abnormal temporal discrimination, are attributed to abnormalities in a brainstem/basal ganglia network for processing *salient sensory environmental and emotional stimuli*, a principal node of which is the superior colliculus. Sleep disorders may be part of this premotor syndrome, but more evidence-based research is needed.

Cervical Dystonia and Its Endophenotype, Abnormal Temporal Discrimination

Adult onset idiopathic isolated focal dystonia (AOIFD), the third-most common movement disorder, is characterized by a number of different phenotypes of which cervical dystonia is the most common.[5] Cervical dystonia is considered genetic in origin, probably autosomal dominant in inheritance with markedly reduced (10-15%) penetrance[6]; recent genetic discoveries account for less than <1% of cases.[7] Most gene carriers remain nonmanifesting throughout life; the majority of cervical dystonia patients appear to have a sporadic, apparently nonfamilial, disorder. The lack of gene discovery has stimulated a search for endophenotypes (subclinical markers of gene carriage, which are not altered by disease penetrance or expression). Many anatomical and functional abnormalities, postulated to be endophenotypes of cervical dystonia, are secondary endophenotypes, developing as a consequence of disease expression. Mediational endophenotypes, found both in cervical dystonia patients and, importantly, in their unaffected relatives, may illuminate pathogenetic mechanisms not obvious from the motor phenotype. Among the many candidates, abnormal

*Correspondence to: Prof. Michael Hutchinson, Newman Clinical Research Professor, St. Vincent's University Hospital, Elm Park, Dublin 4, Ireland; E-mail: mhutchin2@mac.com

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temporal discrimination is considered the most well-defined endophenotype for cervical dystonia.[1]

Abnormal Temporal Discrimination: Subcortical Pathogenetic Mechanisms in Cervical Dystonia

Abnormal temporal discrimination thresholds (TDTs) in cervical dystonia have been demonstrated from many centers over the last 15 years. Early studies used relatively small numbers of participants; in this setting, between-group differences can be detected, but in order to determine whether an individual's TDT is abnormal, a data set from 150 to 200 healthy control participants is needed to cover the age range of 20 to 65 years in both sexes.[8]

It has been proposed that a prolonged TDT indicates disordered subcortical mechanisms for covert attentional orienting, involving processing of salient environmental sensory stimuli through the superior colliculus.[9,10] In support of this concept, a number of structural and functional abnormalities have been demonstrated in unaffected relatives, of patients with cervical dystonia, with abnormal TDTs, compared to relatives with normal TDTs, including: (1) increased putaminal volume measured by voxel-based morphometry[11]; (2) reduced putaminal activation during a functional MRI (fMRI) temporal discrimination task[8]; (3) reduced activation in the superior colliculus in response to a looming visual stimulus by fMRI[12]; (4) impaired GABAergic mechanisms, suggested by sexually dimorphic age-related effects on temporal discrimination.[13] This latter observation is consonant with other reports of reduced gamma-aminobutyric acid (GABA) activity in AOIFD.[14]

Abnormal TDTs show variable age- and sex-related penetrance in unaffected first-degree relatives, being 100% penetrant in women and 40% penetrant in men.[8] It is postulated that abnormal TDTs in cervical dystonia patients and their unaffected relatives represent defective processing of sequential visual (and other sensory) environmental stimuli in a brainstem/basal ganglia network attributed to reduced GABAergic inhibition, both within the superior colliculus and from SNpr.

Although determinable only by laboratory testing, abnormal temporal discrimination, present many years preceding the motor disorder, may be considered as part of the premotor syndrome.

Psychiatric Symptoms in Cervical Dystonia: Prevalence

Of all the nonmotor symptoms in cervical dystonia, including depression, anxiety, and obsessive-compulsive disorders, the most commonly studied psychiatric symptoms are anxiety and depression. In a survey of 1,071 patients with cervical dystonia, 61% said that they suffered depression and mood alterations.[15] The reported prevalence of psychiatric disorder in AOIFD ranges between 12% and 71%, with most studies in the range of 25% to 50%.[16] Validated instruments for depression and anxiety are the most common measures used in clinical surveys; however, in order to fulfill the diagnostic criteria for psychiatric disorder, a structured psychiatric interview is necessary.[16,17]

Psychiatric Symptoms in Cervical Dystonia: A Primary Disorder

Support for the concept that the high prevalence of anxiety and depression in cervical dystonia is not secondary to the movement disorder, but an essential part of the disease phenotype, caused by the same pathogenic mechanisms, comes from a number of observations:

1. Mood disorder *precedes* the onset of cervical dystonia in approximately 70% of patients, sometimes by up to 20 years.[18-21]
2. Mood disorder is more frequent in cervical dystonia than in patients with other chronic disorders such as cervical spondylosis[22] or alopecia areata.[23]
3. The psychiatric disorder persists, despite improvement in the dystonia with botulinum toxin, indicating that it is independent of the motor disorder.[24]
4. In patients with AOIFD and a psychiatric diagnosis, there is an equal sex ratio, whereas in the general population, anxiety and depression are twice as common in women as in men.[16]

The Psychiatry of Cervical Dystonia and Disordered Social Cognition

Our ability to "mentalize," to attribute mental states to others, is the foundation of the concept of social cognition,[25] formally recognized in *The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* as one of six core neurocognitive domains. Social cognition is a multidimensional construct, components of which may be interconnected; it includes: emotional facial recognition, Theory of Mind, social learning, biological motion perception, and empathy.[26] Only a few elements of social cognition have been examined in patients with AOIFD; these few, essentially exploratory, studies indicate an area of research that requires to be addressed.

Biological Motion Perception in Dystonia

Biological motion perception is often claimed to support social cognition; it has been suggested that individuals with higher levels of social traits are better at biological

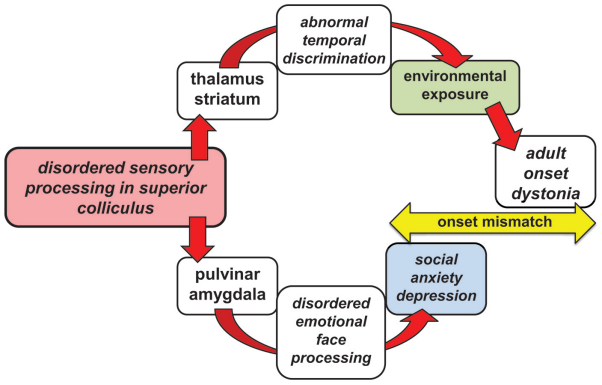

FIG. 1. Illustrating the proposed hypothesis in this article. Disordered sensory processing in the superior colliculus, affecting thalamic and basal ganglia processing, results in abnormal temporal discrimination, which is considered to be an endophenotype for cervical dystonia. The development of adult onset dystonia depends on the type and duration of particular environmental exposures (green box). Most individuals with abnormal temporal discrimination, in the absence of a particular environmental exposure, do not develop cervical dystonia. Because these individuals have disordered sensory processing in the superior colliculus, they may also have defective salient emotional face processing through the collicular-pulvinar-amygdala pathway, and, because of this, we hypothesize that they may be subject to anxiety and depression.

motion perception.[27] Biological motion perception has been found to be defective in patients with writer's cramp[28] and, in a separate study, with cervical dystonia[29]; in both studies, patients exhibited a greater absolute timing error compared to control subjects in the human body motion task, but not in an inanimate object motion task.

Theory of Mind in Cervical Dystonia

Theory of Mind, the ability to understand and interpret the intentions, emotions, and beliefs of others, has been examined in cervical dystonia by only one research group. In 26 nondepressed cervical dystonia patients, there were significant impairments in the Faux Pas Recognition Test; patients (compared to controls) had difficulty in understanding and interpreting the intentions of the story characters.[30] As the researchers indicate, this is an area of research that needs to be pursued.

Defective Emotional Sensory Processing in Adult Onset Focal Dystonia

Only two articles have examined the processing of the emotional content of sensory stimuli in AOIFD. A study of 32 patients (20 with cervical dystonia and 12 with blepharospasm) found that patients had difficulty identifying the facial expression of "disgust" compared to age-matched controls, with nonsignificant trends for impaired recognition of happiness and sadness.[31] Another study of the perception of emotional speech prosody reported deficits in the recognition of angrily intonated words in 30 patients with cervical dystonia, compared to control participants.[32]

The Particularity of the Face: Subcortical Emotional Face Processing and the Amygdala

A face attracts attention and elicits a saccade, even when study participants are instructed to look at non-face stimuli (vehicles); the earliest reliable saccade toward faces can be observed 100 to 110 ms after stimulus onset.[33] The most important information we use to make inferences about the thoughts and intentions of others, based on social cues, is emotional facial expression and, in particular, eye gaze.[34-37] The evaluation of emotional facial expression does not rely on conscious appraisal of the signal; it occurs, in experimental conditions, even when stimuli are masked so that they are not consciously detectable.[36]

The superior colliculus is involved in processing subcortical emotional facial recognition,[34-37] with onward signaling through the pulvinar to the amygdala.[38] Amygdala responses to emotional face stimuli arrive at short latencies, through the magnocellular retinotectal visual pathway and medial pulvinar (Fig. 1).[39,40] Fast emotional face processing with responses in the amygdala at 74 ms has been demonstrated in epilepsy

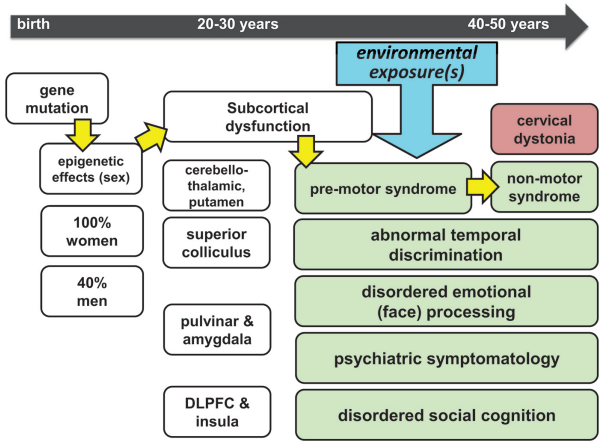

FIG. 2. Diagrammatic illustration of the age- and sex-related effects and environmental exposures affecting the development of cervical dystonia. Sexual epigenetic factors influence penetrance of an abnormal temporal discrimination threshold (100% penetrance in women, 40% penetrance in men). Subcortical dysfunction in the superior colliculus/basal ganglia pathway results in the development of abnormal temporal discrimination. Similar dysfunction in the collicular-pulvinar-amygdala pathway results in disordered salient emotional sensory processing, which is responsible for the development of the premotor syndrome consisting of psychiatric symptomatology and disordered social cognition. Penetrance and expression of adult onset dystonia depends on environmental exposures, which, in the case of cervical dystonia, includes trauma (car accidents and surgeries). Most individuals who inherit a genetic tendency to adult onset dystonia never manifest the disease in the absence of environmental exposure. These individuals may, however, have abnormal temporal discrimination and psychiatric symptomatology affecting their quality of life. The premotorsyndrome may precede the onset of the motor phenotype by many years. DLPFC, dorsolateral prefrontal cortex.

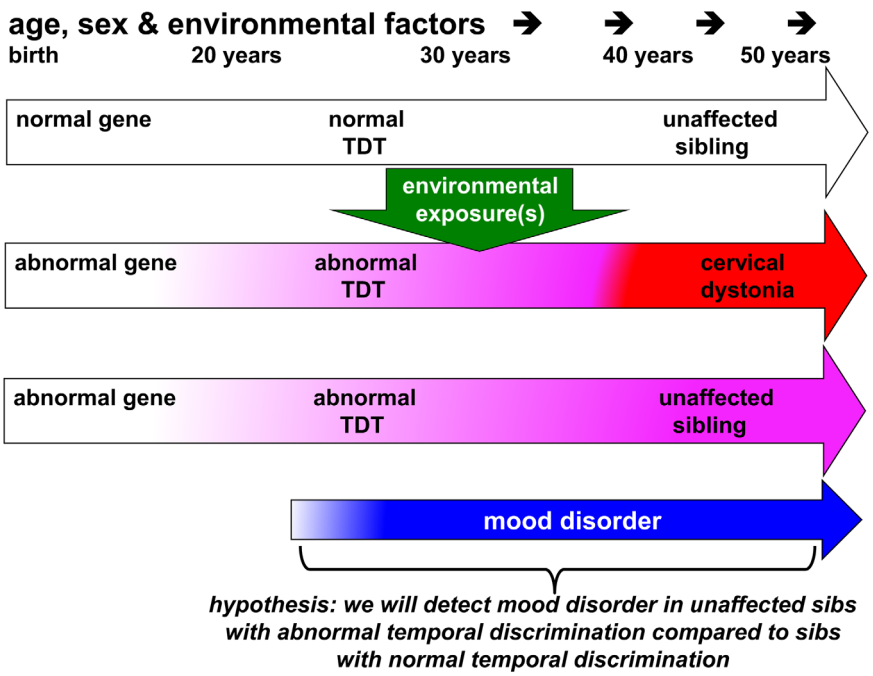

FIG. 3. A diagrammatic illustration of the time course of the onset of abnormal temporal discrimination thresholds in three siblings. One sibling (top arrow) has not inherited the genetic predisposition to cervical dystonia and has normal temporal discrimination. Two siblings (pink arrows) have inherited a genetic predisposition to develop cervical dystonia. The individual (illustrated by the middle arrow) develops abnormal temporal discrimination in their early thirties; he or she experiences an environmental exposure (a car accident) in their midthirties and subsequently develops cervical dystonia in their midforties. Studies from multiple centers (see main text) have demonstrated that these individuals have a long premotor period of mood disorder (often as long as 20 years preceding motor symptom onset; lowest blue arrow). The third individual (lower pink arrow) has inherited a similar genetic predisposition to cervical dystonia and develops an abnormal temporal discrimination threshold in their early thirties, but, in the absence of an appropriate environmental exposure, never develops cervical dystonia; it is hypothesized that this individual will also have a significant mood disorder, detectable by instruments such as the Beck Depression Inventory.

patients being evaluated for temporal lobectomy[41]; in nonhuman primates, pulvinar recordings show 50-ms latency responses to face-like stimuli, including cartoon faces.[42,43] The traditional conception of the function of the amygdala as a "fear hub" (responsive to visual images of fear alone) has been challenged by recent fMRI studies, which have shown that the amygdala was comparably active in response to facial emotional expressions indicating anger, disgust, fear, happiness, and sadness.[44]

Linking Abnormal Subcortical Emotional Processing, Social Cognition, and the Psychiatry of Cervical Dystonia

Two possible hypothetical mechanisms may explain the development of anxiety and depression in cervical dystonia preceding the onset of the motor symptoms of cervical dystonia. Both mechanisms may work together within this subcortical network; this is an area ripe for further study.

a) *The most parsimonious explanation* is that, in individuals who are genetically susceptible to develop cervical dystonia, there is a period of many years when they have reduced cerebral GABA levels both in the superior colliculus (causing abnormal TDTs) and in the amygdala, causing a predisposition to anxiety and depression. GABAergic mechanisms are defective in AOIFD at all levels of the central nervous system[14]; impaired GABAergic function results in amygdala hyperactivity.[45]

b) *The second explanation* relates to intrinsic GABAergic activity within the superficial lamina of the superior colliculus. Blocking GABA receptors in the superficial layers of the superior colliculus causes blunted "onset" and "offset" responses to visual stimuli leading both to disordered sensory processing (postulated to cause abnormal TDTs)[9,10] and increased burst activity in the deeper layers of the superior colliculus, which, through the subcortical pathway, results in excessive stimulation of the amygdala. Stimulation of the deeper layers of the superior colliculus in primates disrupts normal social interactions between pairs of rhesus macaques[46] and anxiety-related responses in rodents.[47]

Conclusions and Implications for Future Studies

We hypothesize that both the premotor/nonmotor syndrome and the motor phenotype in cervical dystonia share common underlying pathogenetic mechanisms involving defective GABAergic inhibition resulting in disordered subcortical processing of salient emotional and sensory stimuli (Fig. 2) manifesting as:

A) The premotor/nonmotor syndrome consisting of:
   (i) Abnormal temporal discrimination attributed to disrupted salient environmental sensory processing in brainstem/basal ganglia networks through the superior colliculus.
   (ii) Anxiety and depression and deficits in social cognition attributed to disordered salient emotional processing in the colicular-pulvinar-amygdala pathway.

B) The motor phenotype (adult-onset dystonia). Particular environmental exposures determine disease penetrance (trauma in cervical dystonia)[48] and expression (hours of writing and focal hand dystonia).[49] In the absence of such exposures (or in the presence of a protective environmental exposure), the motor phenotype may never develop during life.

Future Studies: What Needs to Be Addressed

1) Clinical Practice:

a) A recent study has emphasized the unmet needs of patients with cervical dystonia.[50] Neurologists must address these nonmotor symptoms by active enquiry using recognized validated instruments.

b) The prevalence of neuropsychiatric morbidity in cervical dystonia warrants double-blind, randomized, controlled trials of the use of selective serotonin reuptake inhibitors.

2) Clinical Research:

a) The exploratory studies of components of social cognition, referenced above, need to be replicated in larger cohorts from other centers.

b) The prevalence of mood disorder in unaffected female relatives (with and without abnormal TDTs) of patients with cervical dystonia should be assessed using symptom-based survey measures (Fig. 3).

c) The subcortical pathway for emotional face recognition should be assessed in patients with cervical dystonia and their unaffected relatives with, and without, abnormal TDTs using modern emotional face perception techniques.

Exploration of these hypothetical mechanisms for premotor/nonmotor syndrome in cervical dystonia may enhance our understanding of the pathogenesis of this disorder. ■

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